



Solubility and solution thermodynamics of thymol in six pure organic solvents



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ABSTRACT

The solubility of thymol in methanol, ethanol, 1-propanol, 2-propanol, 1-butanol and acetonitrile with the temperature ranging from (279.15 to 313.15) K at atmospheric pressure was measured by the gravimetric method. For the temperature range investigated, the solubility of thymol in the solvents increased with a rise of temperature. Results of these measurements were correlated by five thermodynamic models—modified Apellblat, λh , van't Hoff, Wilson and NRTL, in which Wilson model achieved the best fitting results. The enthalpy, entropy and Gibbs free energy of dissolution were calculated with the van't Hoff equation. The results indicated that the processes of solution in all selected solvents were endothermic, entropy-driven and non-spontaneous. The studies of molecular simulation and solubility parameters were carried out to give the explanation for the sequence of solubility in various solvents. The data of quasi-static heat capacity for both solid and liquid phases of thymol were investigated by stochastic temperature modulation DSC technique (TOPEM). The extent to which the assumptions of the differential molar heat capacity (ΔC_p) in the regular solution equation influence the magnitude of the ideal solubility of thymol was examined.

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1. Introduction

Solubility, which is one of the most essential physicochemical properties, is commonly useful for the purification and pre-formulation studies of drugs in biological, chemical, pharmaceutical and environmental industries [1]. Hence, accurate solubility data are needed for process and product design. Although there is already a vast amount of literature reporting the results of drug solubility measurement in organic solvents, many more combinations of solvent and solute remain to be investigated.

Thymol (2-isopropyl-5-methylphenol, $C_{10}H_{14}O$, CAS no. 89-83-8, shown in figure 1) is a white crystalline solid, which has been reported to possess anti-microbial [2], anti-inflammatory [3], anti-tumour [4] and fungicide [5] effects. Crystallization step plays an important role in the production

and purification process of thymol. To design an optimized crystallization process, the complete physicochemical data such as solubility and dissolving enthalpy in different solvents are beneficial and the determination of its solubility in different solvents will be useful to choose the appropriate solvent. Yet the solubility data of thymol in most of solvents have not been known.

In this work, the solubility of thymol in methanol, ethanol, 1-propanol, 2-propanol, 1-butanol and acetonitrile at temperatures ranging from (279.15 to 313.15) K at atmospheric pressure were measured by the gravimetric method. The experimental results were correlated by five thermodynamic models—modified Apellblat, λh , van't Hoff, Wilson and NRTL. Using the van't Hoff equation, the thermodynamic functions (Gibbs free energy, enthalpy, and entropy of solution) were calculated. Further studies about molecular simulation and solubility parameters were carried out to interpret the sequence of solubility in the selected solvents. Finally, the molar heat capacities of thymol for both solid and liquid phases were measured at a temperature range around its melting point via the stochastic temperature modulation DSC technique (TOPEM) [6]. The ideal solubility of thymol was predicted by

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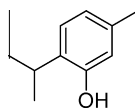


FIGURE 1. Molecular structure of thymol.

the regular solution equation with assumptions of $\Delta C_p = 0$, entropy of fusion $\Delta_{\text{fus}}S$ or differential molar heat capacity at the melting point of thymol, respectively. The accuracy of prediction could be promoted by taking the experimental value of ΔC_p .

2. Experimental

2.1. Materials

Thymol was supplied by the Aladdin Industrial Corporation, Shanghai, China with the purity of the mass fraction higher than 0.998 and used without further purification. The methanol, ethanol, 1-propanol, 2-propanol, 1-butanol and acetonitrile used for dissolving the thymol were of analytical reagent (AR) grade (purchased from the Tianjin Jiangtian Chemical Technology Co., Ltd., China) with a mass fraction purity of higher than 0.995 without further purification. The details of the materials used in this work are listed in table 1.

2.2. Procedure of DSC and TOPEM

Before the analysis, the Mettler-Toledo DSC 1/500 was calibrated with indium and zinc standards. The enthalpy of fusion and melting temperature of thymol were determined by the fusion signal analysis. Approximately (0.005 to 0.010) g of thymol was weighed by an electronic analytical balance (Mettler-Toledo AB204-N) with the accuracy of ± 0.0001 g and added into a hermetically sealed aluminum DSC pan. The sample was heated under a nitrogen atmosphere ($2.5 \text{ mL} \cdot \text{s}^{-1}$) from $T = (298.15 \text{ to } 353.15) \text{ K}$ at a heating rate of $T = 2 \text{ K} \cdot \text{min}^{-1}$. The standard uncertainty for the melting temperature was 0.5 K, and the relative standard uncertainty for enthalpy of fusion was 0.02.

In addition to the total heat flow given by traditional DSC, TOPEM can separate the measured heat flow into two components, the smeared sensible heat flow and the latent heat flow component from the heat flow responding to the small amplitude temperature modulations superimposed on a constant underlying heating rate.

TABLE 1

Information on source and purity (mass fraction) of the materials used in the experiments.

| Chemical name | Source | Mass purity | Analysis method |
|---------------|---|-------------|-------------------|
| Thymol | Aladdin Industrial Co., Shanghai, China | >0.998 | HPLC ^a |
| Methanol | Jiangtian Chemical Technology Co., Ltd., Tianjin, China | >0.995 | AR ^b |
| Ethanol | Jiangtian Chemical Technology Co., Ltd., Tianjin, China | >0.995 | AR ^b |
| 1-propanol | Jiangtian Chemical Technology Co., Ltd., Tianjin, China | >0.995 | AR ^b |
| 2-propanol | Jiangtian Chemical Technology Co., Ltd., Tianjin, China | >0.995 | AR ^b |
| 1-butanol | Jiangtian Chemical Technology Co., Ltd., Tianjin, China | >0.995 | AR ^b |
| Acetonitrile | Jiangtian Chemical Technology Co., Ltd., Tianjin, China | >0.995 | AR ^b |

^a High-performance liquid chromatography.

^b Analytical reagent.

By analysing the correlation between the heating rate and heat flow, information on the dynamic behavior of the sample and the instrument are determined. Corresponding to sensible and latent heat flow the quasi-static heat capacity can be obtained without additional calibration procedures [7]. If the measurement is performed under almost linear and stationary conditions, agreement between the reversing and sensible heat flow and between the non-reversing and latent heat flow improves. Such conditions can be achieved with small temperature perturbation and sufficiently low underlying heating rates [8].

The temperature pulse was set at 0.5 K and the constant heating rate at $T = 0.5 \text{ K}$ for TOPEM. With TOPEM measurements at a relative low underlying heating rate, the response shows linear behavior. The random pulse width was set as 15 s to 30 s. The experimental measurements to obtain the solid and liquid heat capacity ($C_{p,\text{solid}}$ and $C_{p,\text{liquid}}$, shown in figure S1 of the supporting information) of pure thymol were performed at a temperature far away from its melting point. The solid heat capacity data were obtained from $T = (283.15 \text{ to } 303.15) \text{ K}$, whereas liquid heat capacity values were measured at temperatures ranging from (343.15 to 363.15) K. All the data collection and analysis were carried out by Mettler-Toledo's STARe software. The standard uncertainty for the temperature was 0.05 K, and the relative standard uncertainty for the heat capacity was 0.03.

2.3. Solubility measurement

The gravimetric method [9] was employed to determine the solubility of thymol. Excess amounts of thymol crystals were added to 30 mL of organic solvents (methanol, ethanol, 1-propanol, 2-propanol, 1-butanol and acetonitrile) in the 50 mL Erlenmeyer flasks. Temperature ranging from (279.15 to 313.15) K which was controlled by the thermostat in the shaker when above $T = 298.15 \text{ K}$ and connected to the CF41, Julabo, Seelbach, Germany to keep the water bath temperature at a constant value when below 298.15 K. The variation of system temperature for all the measurements was within $\pm 0.05 \text{ K}$. In the incubator shaker the suspension was kept shaken to ensure the adequate dissolution of the solute and lasted for about 24 h to reach equilibrium. Then turned off the swing and stood for 12 h to settle down the undissolved thymol. After that, about 3 mL supernatant liquid was taken out quickly and filtered through a $0.25 \mu\text{m}$ PTFE filter then poured into the small beaker which had been previously weighed by the AB204-N with a standard uncertainty of ± 0.0001 g. All the PTFE filters had been placed in the solution's temperature before they were used. Owing to the fact that it is the liquid supernatant that been taken out, the degree of preciseness for experimental values could be guaranteed as long as there were no solids precipitate or solvent evaporate. The total weight of the beaker and solution was recorded immediately and denoted as m_1 . The filtered samples were placed in the Vacuum drying oven until no mass change was observed while weighing the final total weight m_2 . Then the mass of the solute and solvent quantity in the saturated solution can be obtained. The saturated mole fraction solubility of solute x_1 can be obtained as follows:

$$x_1 = \frac{(m_2 - m_0)/M_1}{(m_2 - m_0)/M_1 + (m_1 - m_2)/M_2} \quad (1)$$

where m_0 represents the mass of the empty beaker and M_1 and M_2 represent the molar mass of the solute thymol crystal and the solvent, respectively.

The same solubility experiment was repeated three times. The uncertainties of the experimental solubility values were less than 2% which resulted from the uncertainties in the temperature mea-

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